DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 1-15, in the reply filed on July 31, 2008 is acknowledged. Applicant's have further elected SEQ ID NO: 1 in the reply filed on December 1, 2008. Claims 16-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 2, 7, 10, 14 and 15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 2 and 7, the term "preferably" renders the claim indefinite because it is unclear whether the limitations following the phrase are part of the claimed invention. See MPEP § 2173.05(d).

Claim 10 includes the term "DD-RT-PCR". There is no strict definition of DD-RT-PCR in the claims or specification, particularly with regard to "DD", and it is not clear what form of RT-PCR is used in the method. For examination purposes, the term will be interpreted as meaning differential display reverse-transcription PCR.

Regarding claim 14, the phrase "or sequences deriving thereof" renders the claim indefinite because it is unclear what sequences are claimed. It cannot be determined what variations of SEQ ID NO:1 are encompassed. Clarification is required.

Claim 15 includes the limitation “wherein said SmRNA is reverse transcribed into cDNA of SEQ ID NO: 3 using a pair of primers consisting of SEQ ID NO: 5 and SEQ ID NO: 6", yet based on the sequence of the SmRNA and the primer binding sites of SEQ ID NOS: 5 and 6, the resulting product would contain only a fragment of SEQ ID NO: 3, and therefore it is not clear how using the primers results in reverse transcription into SEQ ID NO: 3.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-4, 6, 7 and 9-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Andrieu et al. (U.S. Patent No. 6,277,560).

Andrieu teaches a method of normalizing products of a reverse transcription reaction of mRNA extracted from different biological samples (for overview, see Abstract and column 3, lines 18-30), wherein said method comprises the steps consisting of

a) adding a synthetic messenger RNA (SmRNA) which does not compete with the reverse transcription of target mRNAs of said sample and which do not interfere with the reverse transcription of endogenous mRNA of said sample to a reaction mixture comprising total RNA extracted from said sample (an internal control, IC, is added to an amplification reaction containing sample RNA targets, and the IC is in the form of transcript RNA and is not related to the target RNA with regard to sequence or primer binding sites, column 4, lines 47-55; for specific example of HIV detection using IC, see Example 10, column 17, lines 12-25);

b) determining the reverse transcription efficacy p for the SmRNA (the efficiency of reverse transcription of the IC is determined based on the amount of IC added to the reaction, column 3, lines 20-24; for HIV detection, amount of internal control is determined using IC-specific probe, column 18, lines 48-63) and,

c) adjusting the level of target mRNA transcripts by multiplication with p (the quantity of transcripts in an unknown sample is compared to that determined for known quantities of the IC to quantify the amount of the unknown sample, column 3, lines 25-30; for HIV detection, the numbers of HIV particles in each sample are determined

based on standard curve generated from HIV standards and normalized based on the amplification efficiency of the IC, column 18, lines 48-63).

With regard to claims 2 and 3, Andrieu teaches a method wherein a SmRNA displaying less than 95%, 97% or 99% or preferably less than 99.50% identity with any mRNA of said sample and is unable to hybridize under stringent conditions with any mRNA of said sample, is used to perform a non-competitive reverse transcription reaction and to calibrate the quantity of each target mRNA obtained after amplification with the quantity of the cDNA amplified corresponding to said SmRNA (an internal control in the form of a heterologous transcript RNA that is not related to the target RNA is added to the RT-PCR reaction, column 4, lines 47-52).

With regard to claims 4 and 6, Andrieu teaches a method wherein the SmRNA comprise a segment, including a polyA segment, which is non-homologous to the target mRNA and is devoid of sequences complementary to the primer sequences used to amplify the target mRNA (the IC is a heterologous transcript RNA unrelated to the target RNA and uses a different primer set for amplification than that of the HIV target, column 4, lines 47-52 and column 17, lines 12-25).

With regard to claim 7, Andrieu teaches a method wherein said SmRNA is about 80 nucleotide long or longer, preferably about 100 nucleotide long (the IC may be heterologous plasmid DNA or transcript RNA and therefore larger than 80 nucleotides, column 4, lines 47-52).

With regard to claims 9-12, Andrieu teaches a method consisting of non-competitive RT-PCR or DD-RT-PCR wherein quantification of target mRNAs is performed by means of normalization with said SmRNA (the IC included in the RT-PCR reaction is used to measure amplification efficiency, which is used to determine the numbers of HIV particles per ml of each plasma/serum sample, column 17, lines 23-25 and column 18, lines 63-67) and which may be performed on DNA microarrays wherein the cDNA corresponding to the SmRNA is amplified and spotted onto said microarrays (post-reaction mixtures containing sample and IC RNA are mixed with specific HIV and IC detection probes and added to a microplate for detection using an immuno-based chemoluminescence assay, column 18, lines 48-63).

With regard to claim 13, Andrieu teaches a method consisting of Northern blotting wherein said SmRNA is pooled with samples (amplification products can be separated by electrophoresis on agarose gels, column 11, lines 35-42, and detected using probes that specifically hybridize to IC and HIV cDNA column 17, lines 30-34).

6. Claims 1-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Cleland et al. (Vox Sang (1999) 76:170-174).

Cleland teaches a method of normalizing products of a reverse transcription reaction of mRNA extracted from different biological samples (for overview, see Abstract), wherein said method comprises the steps consisting of

a) adding a synthetic messenger RNA (SmRNA) which does not compete with the reverse transcription of target mRNAs of said sample and which do not interfere with the reverse transcription of endogenous mRNA of said sample to a reaction mixture comprising mRNA extracted from said sample (an internal control RNA virus sample, bovine viral diarrhea virus, BVDV, is added to an amplification reaction containing sample HCV RNA targets, and is not related to the target HCV RNA with regard to sequence or primer binding sites, p. 171, column 1, lines 4-13 and Table 1);

b) determining the reverse transcription efficacy p for the SmRNA (dilutions of BVDV were added to RT-PCR reactions alone and with HCV target samples and amplified using BVDV-specific primers, p. 171, column 2, line 32 to p. 172, column 1, line 13 and column 2, lines 2-4) and,

c) adjusting the level of target mRNA transcripts by multiplication with p (the use of the internal control, BVDV RNA, for detection of HCV by RT-PCR serves as a positive control for both extraction and amplification steps to allow the relative efficiencies of the amplification for both sequences to be adjusted so that the assay can detect down to single molecules of HCV cDNA, p. 172, column 2, line 30 to p. 173, column 1, line 2 and p. 173, column 2, line 4 to p. 174, column 1, line 5).

With regard to claims 2 and 3, Cleland teaches a method wherein a SmRNA displaying less than 95%, 97% or 99% or preferably less than 99.50% identity with any mRNA of said sample and is unable to hybridize under stringent conditions with any mRNA of said sample, is used to perform a non-competitive reverse transcription reaction and to calibrate the quantity of each target mRNA obtained after amplification with the quantity of the cDNA amplified corresponding to said SmRNA (the amplified regions of BVDV RNA have similar physicochemical properties to HCV but no nucleotide similarity to HCV, p. 171, column 2, lines 11-16).

With regard to claim 4, Cleland teaches a method wherein the SmRNA comprise a segment which is non-homologous to the target mRNA and is devoid of sequences complementary to the primer sequences used to amplify the target mRNA (the amplified regions of BVDV RNA and HCV RNA have no nucleotide similarities, particularly in the primer binding regions used for RT-PCR, p. 171, column 2, lines 11-16, p. 173, column 2, line 4 to p. 174, column 1, line 1 and Table 1).

With regard to claim 5, Cleland teaches a method wherein said SmRNA is added in different reaction mixtures comprising one sample in different dilutions (dilutions of RNA extracted from BVDV were added to RT-PCR reactions and plasma samples to establish standard curves for estimating genome equivalents of target sequences in amplification and extraction steps, p. 171, column 2, line 32 to p. 172, column 1, line 32 and Table 2).

With regard to claims 6 and 7, Cleland teaches a method wherein said SmRNA is about 80 nucleotide long or longer, preferably about 100 nucleotide long, and comprises a polyA segment (total RNA extracted from a replicating culture of BVDV serves as the internal control, p. 171, column 2, lines 32-33).

With regard to claim 8, Cleland teaches a method wherein said SmRNA is specifically amplified with a pair of primers designed to avoid primer dimerization (nested primer pairs are used to successfully perform RT-PCR reactions and do not display homologies that would lead to primer-dimer formation, p. 171, column 2, line 33 to column 1, line 8 and Table 1).

With regard to claim 9, Cleland teaches a method consisting of non-competitive RT-PCR wherein quantification of target mRNAs is performed by means of normalization with said SmRNA (the use of the internal control, BVDV RNA, for detection of HCV by RT-PCR serves as a positive control for both extraction and non-competitive RT-PCR amplification steps to allow the relative efficiencies of the amplification for both sequences to be adjusted, p. 173, column 2, line 4 to p. 174, column 1, line 5).

Allowable Subject Matter

7. Claims 14 and 15 are free of the prior art, but are rejected for other reasons. No prior art was found that teaches or suggests a method wherein said SmRNA consists of

a SEQ ID NO: 1 and wherein said SmRNA is reverse transcribed into cDNA of SEQ ID NO: 3 using a pair of primers consisting of SEQ ID NOS: 5 and 6.

Conclusion

8. Claims 1-15 are rejected.

Correspondence

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637